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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel quinolyl-thienyl chalcones and their 2-pyrazoline derivatives with diverse substitution pattern as antileishmanial agents against *Leishmania major*

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Abstract A series of twenty-two new pyrazoline derivatives was prepared from quinoline-based chalcones which in turn were synthesized by condensing formylquinolines with diverse acetylthiophenes. The titled compounds were characterized by spectroscopic techniques (NMR, IR and MS) and elemental analysis. All the compounds were screened for antileishmanial activities. Compounds **1e**, **1f**, **2a**, **2c**, **2d**, **2g**, **2k**, and **4a** were found potentially active antileishmanial agents. Bioassay results show that the type and positions of the substituents seem to be critical for their antileishmanial activities.

Keywords Chalcones · Pyrazolines · Antileishmanial activity · Formylquinolines · Acetylthiophenes

Introduction

1,3-Diaryl-2-propen-1-ones (chalcones) are one of the most important classes of natural products, and are widespread in the plant kingdom. Chalcones (natural or synthetic) possess a broad spectrum of biological activities including anti-inflammatory (Ballesteros *et al*.,1995), antifungal (Nowakowska, 2007), antioxidant (Mukherjee *et al*., 2001), antimalarial (Wu *et al*., 2002), antituberculosis (Sivakumar *et al*., 2007), analgesic (Viana *et al*., 2003), antitumor (Shibata, 1994), anticancer (Wattenberg *et al*., 1994), antiviral (Trivedi *et al*., 2007), anti-AIDS (Wu *et al*., 2003) and antileishmanial agents (Boeck *et al*., 2006).

Pyrazoline derivatives of chalcones have been reported to possess a widespread range of biological activities like antibacterial (Nauduri and Reddy, 1998), antifungal (Azarifar and Shaebanzadeh, 2002), antidepressant (Bilgin *et al*., 1993), antitumor (Taylor and Patel, 1992), antimicrobial (Ramalingham *et al*., 1977), anti-inflammatory, molluscicidal activity (Barsoum *et al*., 2006), antiamoebic (Budakoti *et al*., 2006), anticonvulsant activities (Ozdemir *et al*., 2007). One of the most famous pyrazole-based drugs used as a non-steroidal anti-inflammatory drug (NSAID) is celecoxib (Fig. 1) (Rezende, *et al*., 2010). Considerable attention has been focused on the pyrazoline family in the last two decades. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline-type compounds (Lévai, 2005). After the pioneering work by Fischer and Knövenagel in the late nineteenth century, the reaction of α,β-unsaturated aldehydes and ketones with hydrazines became one of the most popular methods for the preparation of 2-pyrazolines (Lévai *et al*., 2004).

Quinolines and their derivatives, which represent a major class of heterocycles (Meth-Cohn and Narine, 1978) and are widely found in natural products (Michael 2003, 2004) and drugs (Alhaider *et al*., 1985; Campbell *et al*., 1988; Du, 2003), exhibit significant role in medicinal chemistry. Several quinoline derivatives have been reported to exhibit bactericidal (Awad *et al*., 1991), antimalarial (Ginsburg *et al*., 1999), antiallergenic (Althuis *et al*., 1980) and anti-inflammatory (Dillard *et al*., 1973) properties. Some of the famous antimalarial drugs, containing quinoline ring system; available in the market are plasmoquine

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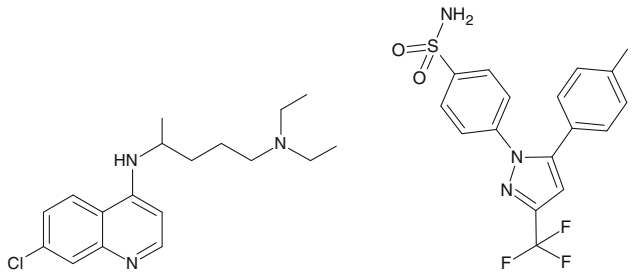


Chloroquine (Antimalarial) Celecoxib (NSAID)

Fig. 1 Structures of a quinoline and a pyrazole-based drugs

(Manske and Kulka, 1953), primaquine and chloroquine (Singh *et al*., 1978). Many quinoline derivatives are found to possess anticancer and antitumor activities (Loaiza *et al*., 2004). Among the quinolines, 2-chloro-3-formylquinolines find an important place in synthetic organic chemistry, as these are key intermediates for further β-annelation of a wide variety of ring systems and for the inter-conversions of many functional groups (Meth-Cohn, 1993).

In this study, the 2-chloro-7/8-methyl-3-formylquinoline nucleus and chalcone functionality have been incorporated in a single molecule (**1a–k** and **2a–k**). Then each of the prepared chalcones was refluxed with hydrazine hydrate in ethanol to yield twenty-two novel 2-pyrazolines (**3a–k** and **4a–k**) based on quinolyl-thienyl ring systems. Finally, all the title compounds were tested for their antileishmanial activities.

Results and discussion

Chemistry

The two precursors, 2-chloro-3-formyl-7- and 8-methyl-quinoline were prepared by reported method (Meth-Cohn *et al*., 1981). Synthesis of the chalconess (**1a–k** and **2a–k**) was based on Claisen-Schmidt condensation (Li *et al*., 1995). For this purpose, the prepared formyl quinolines were condensed with commercially available acetyl thiophenes (Table 1), in the presence of sodium hydroxide. Finally, chalcones thus prepared, on cyclization with hydrazine hydrate, gave the corresponding 2-pyrazoline derivatives (**3a–k** and **4a–k**) in a reasonably good yield (Scheme 1).

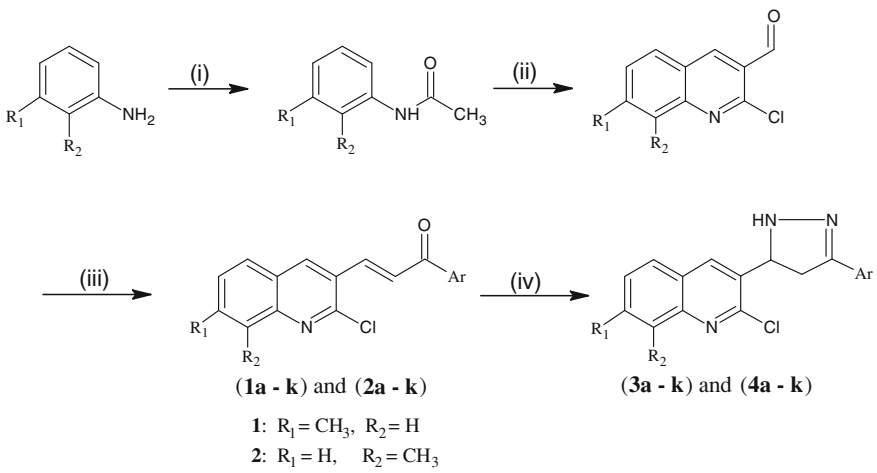
Spectral data (IR, ^{1}H-NMR and MS) of all the newly synthesized compounds were found in good agreement with the proposed structures. IR spectra of the compounds **1a–k** and **2a–k** showed an absorption band at 1650 cm^{-1}, typical of the stretching vibrations of chalcone moiety. No

Table 1 Aryl moiety (Ar) in chalcones (**1a–k**) and (**2a–k**)

Ketones	Ar
a	C_4H_3S-3-yl
b	3-$CH_3C_4H_2S$-2-yl
c	4-$CH_3C_4H_2S$-2-yl
d	5-$CH_3C_4H_2S$-2-yl
e	2,5-diCH_3C_4HS-3-yl
f	3-ClC_4H_2S-2-yl
g	5-ClC_4H_2S-2-yl
h	2,5-diClC_4HS-3-yl
i	3-BrC_4H_2S-2-yl
j	5-BrC_4H_2S-2-yl
k	5-IC_4H_2S-2-yl

peaks were found due to starting material aldehydic functionality as impurity. In the ^{1}H-NMR spectra of the chalcones (**1a–k** except **1e**, **1f** and **1i**) and (**2a–k** except **2e**, **2f** and **2i**), two very sharp doublets around δ 7.40 ppm for H_α and δ 8.20 ppm for H_β, with J-value 15–16 Hz for the *trans* chalcones were exhibited. Interestingly, in chalcones **1e** and **2e**, H_α and H_β showed a doublet in the upfield at δ 7.33–7.32 and 8.10–8.08 ppm, respectively. This may be attributed to an additional +I effect induced by CH_3 group present in the close vicinity. Similarly, in chalcones (**1f**, **1i**, **2f** and **2i**), H_α revealed a doublet relatively in the downfield at δ 7.82–7.81 ppm. This may be attributed to an additional −I effect due to Cl/Br in the vicinity. The molecular ion observed in the mass spectra for all the chalcones confirmed their molecular masses. The base peak, in the mass spectra of most of the chalcones, was obtained possibly by the cleavage of HC–CO bond in the chalcone moiety. While in bromo- and iodo-substituted chalcones (**1i–1k** and **2i–2k**), the base peak is due to the cleavage of two bonds, i.e. CO—thiophenyl and Br/I—thiophenyl bonds. The *E*-configuration was confirmed by X-ray structure of two similar structured chalcones which were already reported (Rizvi *et al*., 2008).

Similarly, in case of 2-pyrazolines (**3a–k** and **4a–k**), IR spectra of all the compounds did not show absorbance at 1650 cm^{-1} which confirmed the absence of the chalcone moiety. A new peak with absorption band at 3280 cm^{-1} was revealed due to NH of 2-pyrazoline ring. ^{1}H-NMR spectra of the pyrazolines (**3a–k** and **4a–k**) ascertained the presence of two doublets of doublet signals due to CH_2 protons H_α (upfield H of CH_2) at δ 2.82–3.21 ppm region and H_β (downfield H of CH_2) at δ 3.64–4.10 ppm, respectively. The CH proton appeared as a triplet at δ 5.28–5.40 ppm region. The molecular ion M^+, observed in the mass spectra for all the pyrazolines confirmed their molecular masses. The base peak, in almost all the mass spectra (except for **3f**), was exhibited by M^+ itself.



Scheme 1 Reaction protocol for the synthesis of 2-pyralozine derivatives (**3a–k**) and (**4a–k**) (*i*) AcOH, H_3PO_4, reflux, 4–6 h, (*ii*) $POCl_3$, DMF, 80°C, (*iii*) **a–k**, NaOH, rt, 2 h, (*iv*) Hydrazine, EtOH, reflux

Antileishmanial activity

According to the results obtained, structure–activity relationship among the two series of chalcones (**1a–k** and **2a–k**) may be explained in terms of stereo- and electronic and/or steric properties (see Fig. 2).

For example, the unsubstituted thiophenyl derivatives (**1a** and **2a**) have prominent difference in antileishmanial activities, i.e. **2a** is more active than **1a** ($IC_{50} = 0.88 \pm 0.20$ μg/ml for **1a** and $IC_{50} = 0.61 \pm 0.81$ μg/ml for **2a**), while the activity decreased considerably by the introduction of CH_3 group at position 3 of thiophenyl ring (**1b** and **2b**; Table 2) perhaps due to steric effect, whereas, the activity is relatively increased on moving the methyl substituent to position 4 (**1c** and **2c**) or 5 (**1d** and **2d**) impairing the steric effect. Conversely, replacing the methyl group by chloro group at position 3 of thiophenyl ring (**1f** and **2f**) results in enhanced activity. This may be attributed to the greater electronic effect of chloro group, while the steric effect of bromo group overweighs the electronic effect at position 3 of thiophenyl ring (**1i** and **2i**). Moreover, substituting the halogen atoms (Cl, Br and I) at position 5 of thiophenyl ring (**1g**, **1j**, **1k**, **2g**, **2j** and **2k**) deactivates these compounds due to the absence of electronic effect stereochemically. Similarly, 2,5-disubstituted methyl derivatives (**1e** and **2e**) displayed more activity than their dichloro analogs (**1h** and **2h**). This may be attributed to the possibility of existence of electronic effect which is due to the dipolar repulsive forces as shown in Fig. 2d by curved arrow (iii). While, there is no such electronic or steric effect in dimethyl derivatives (**1e** and **2e**).

It is quite obvious from Table 2 that conversion of both series of chalcones (**1a–k** and **2a–k**) to their corresponding 2-pyrazoline derivatives (**3a–k** and **4a–k**) results in an overall decrease in the antileishmanial activity. This fact clearly indicates the significance of chalcone moiety

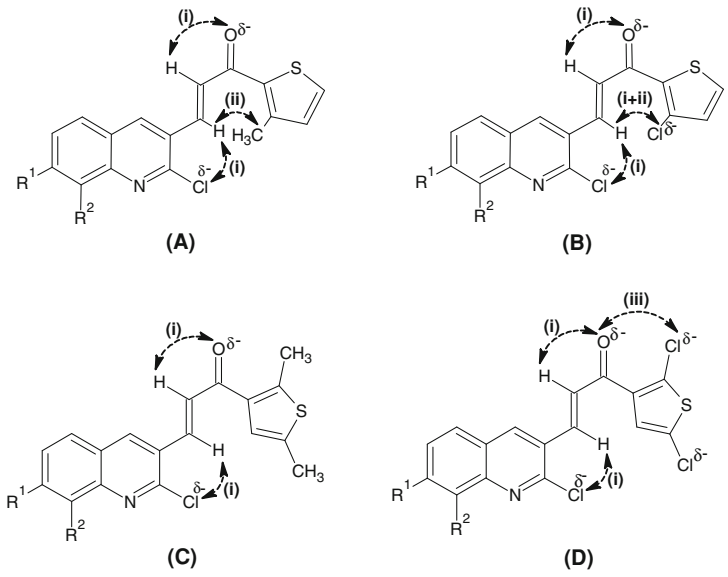


Fig. 2 Proposed stereo-, electronic and/or steric properties (*i*) electronic effect (attractive forces), (*ii*) steric effect; (*iii*) electronic effect (dipolar repulsive forces)

Table 2 Antileishmanial activity of series **1a–k**, **2a–k**, **3a–k** and **4a–k** (IC_{50} values)

Compounds	IC_{50} (μg/ml)
1a	0.88 ± 0.20
1b	0.92 ± 0.11
1c	0.83 ± 0.05
1d	0.74 ± 0.31
1e	0.62 ± 0.24
1f	0.59 ± 0.20
1g	0.81 ± 0.09
1h	0.78 ± 0.14
1i	0.71 ± 0.18
1j	0.91 ± 0.31
1k	0.84 ± 0.22
2a	0.61 ± 0.81
2b	0.94 ± 0.10
2c	0.59 ± 0.09
2d	0.61 ± 1.25
2e	0.73 ± 0.08
2f	0.78 ± 0.15
2g	0.65 ± 0.14
2h	0.85 ± 0.18
2i	0.93 ± 0.99
2j	0.78 ± 0.032
2k	0.67 ± 0.23
3a	0.94 ± 0.02
3b	0.76 ± 0.05
3c	0.87 ± 0.08
3d	0.89 ± 0.03
3e	0.76 ± 0.19
3f	0.78 ± 0.07
3g	0.83 ± 0.50
3h	0.71 ± 0.45
3i	0.85 ± 0.18
3j	0.93 ± 0.62
3k	0.88 ± 0.27
4a	0.67 ± 0.09
4b	0.78 ± 0.23
4c	0.74 ± 0.09
4d	0.89 ± 0.10
4e	0.93 ± 0.16
4f	0.84 ± 0.07
4g	0.75 ± 0.02
4h	0.79 ± 0.03
4i	0.94 ± 0.20
4j	0.93 ± 0.20
4k	0.77 ± 0.02
Standard drug MIC(μg/ml ± SD) (Amphotericin B)	0.56 ± 0.20

towards antileishmanial activity in the titled compounds. In Fig. 2, this is proposed to be due to electronic effect shown by curved arrows, labelled as (i), which is vanished by the ring-closure at chalcones moiety.

Conclusion

It is evident from the above discussion that the chalcones (**1a–k** and **2a–k**) exhibited more activity than their corresponding pyrazoline derivatives (**3a–k** and **4a–k**). We divided the compounds into four categories for their antileishmanial activities and represrented in Table 3, i.e. IC_{50} = 0.59–0.56 μg/ml or below as significantly active, 0.69–0.60 μg/ml as good activity, 0.79–0.70 μg/ml as moderately active and 0.95–0.80 μg/ml as low activity. The compounds **1e**, **1f**, **2a**, **2c**, **2d**, **2g**, **2k** and **4a** were found potentially active antileishmanial agents.

Experimental

General

Melting points were taken on Gallenkamp melting point apparatus and remained uncorrected. IR spectra were recorded in KBr pellets on Perkin Elmer infrared spectrophotometer. ^1H NMR spectra were performed in $CDCl_3$ on Brücker/XWIN NMR (400 MHz) and TMS was used as internal standard (chemical shifts, δ in ppm) unless otherwise specified. Mass spectra were recorded on a Jeol MSRoute instrument. Thin layer chromatography (TLC) was performed with aluminium sheets-Silica gel 60 F254 purchased from Merck. Purification of synthesized compounds was made by recrystallization from appropriate solvents. Reagent grade chemiocals such as phosphoryl chloride, acetyl thiophenes, *o*-toluidine, *m*-toluidine, *N*,*N*-dimethylformamide and hydrazine hydrate (Aldrich and Alpha Aesar) were used as received. Elemental analyses were performed by C.S.I.C., Madrid Spain and were within ±0.4% of predicted values for all compounds.

*General procedure for the preparation of (2E)-3-(2-chloro-7/8-methylquinolin-3-yl)-1-(Ary) prop-2-en-1-ones (**1a–k**) and (**2a–k**)*

The two precursors, 7/8-methyl-substituted 2-chloro-3-formylquinolines were synthesized following literature method (Meth-Cohn *et al*., 1981). A mixture of formylquinoline (10 mmol) and an aromatic ketone (10 mmol) in methanol (50 ml) was stirred at room temperature,

Table 3 Proposed categories of antileishmanial agents

Category	Compounds
Significant	**1f**, **2c**
Good	**1e**, **2a**, **2d**, **2g**, **2k**, **4a**
Moderate	**1d**, **1h**, **1i**, **2e**, **2f**, **2j**, **3b**, **3e**, **3f**, **3h**, **4b**, **4c**, **4g**, **4h**, **4k**
Low	**1a–1c**, **1g**, **1j**, **1k**, **2b**, **2h**, **2i**, **3a**, **3c**, **3d**, **3g**, **3i–3k**, **4d–4f**, **4i**, **4j**

followed by dropwise addition of aq. NaOH (4 ml, 10%). The stirring was continued for 2 h and the reaction mixture was then kept at 0°C for 24 h. Subsequently, it was poured onto ice-cold water (200 ml). The precipitates were collected by filtration, washed with cold water followed by cold MeOH. The resulting chalcones were recrystallized from $CHCl_3$ and dried in vacuo.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-thien-3-ylprop-2-en-1-one ***(1a)*** Yield, 65%; colourless solid. mp 180–182°C. IR (KBr, cm^{-1}): 1649 (C=O), 1594 (C=C), 1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s, Me), 7.39 (1H, dd, H_4', $J = 5.1$ Hz, 2.9 Hz), 7.42 (1H, dd, H_5, $J = 8.2$ Hz, 1.2 Hz), 7.45 (1H, d, H_α, $J = 15.7$ Hz), 7.69 (1H, dd, H_5', $J = 5.1$ Hz, 1.0 Hz), 7.76 (1H, d, H_6, $J = 8.3$ Hz), 7.79 (1H, s, H_8), 8.19 (1H, d, H_β, $J = 15.6$ Hz), 8.20 (1H, dd, H_2', $J = 2.9$ Hz, 1.0 Hz), 8.42 (1H, s, H_4). MS (*m/z*): 313 (M^+, 1.86%), 111 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{17}H_{12}ClNOS$: C, 65.07; H, 3.85; N, 4.46. Found: C, 65.03; H, 3.76; N, 4.43.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(3-methylthien-2-yl) prop-2-en-1-one ***(1b)*** Yield, 51%; pale yellow solid. mp 208–210°C. IR (KBr, cm^{-1}): 1653 (C=O), 1594 (C=C), 1563 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56–2.66 (s, 2× Me), 7.02 (1H, d, H_4', $J = 4.9$ Hz), 7.40 (1H, d, H_α, $J = 15.4$ Hz), 7.42 (1H, dd, H_5, $J = 8.2$ Hz, 1.3 Hz), 7.49 (1H, d, H_5' $J = 4.9$ Hz), 7.77 (1H, d, H_6, $J = 8.6$ Hz), 7.78 (1H, s, H_8), 8.18 (1H, d, H_β, $J = 15.4$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 327 (M^+, 10%), 125 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.92; H, 4.25; N, 4.25.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(4-methylthien-2-yl)prop-2-en-1-one ***(1c)*** Yield, 56%; yellow solid. mp 173–174°C. IR (KBr, cm^{-1}): 1655 (C=O), 1594 (C=C), 1564 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.33–2.56 (s, 2× Me), 7.31 (1H, s, H_5'), 7.42 (1H, dd, H_5, $J = 8.2$ Hz, 1.3 Hz), 7.44 (1H, d, H_α, $J = 15.5$ Hz), 7.71 (1H, s, H_3'), 7.76 (1H, d, H_6, $J = 8.3$ Hz), 7.79 (1H, s, H_8), 8.21 (1H, d, H_β, $J = 15.6$ Hz), 8.42 (1H, s, H_4). MS (*m/z*): 327 (M^+, %), 125 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.85; H, 4.24; N, 4.23.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(5-methylthien-2-yl)prop-2-en-1-one ***(1d)*** Yield, 52%; pale yellow solid. mp 173–175°C. IR (KBr, cm^{-1}): 1652 (C=O), 1595 (C=C), 1563 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56–2.57 (s, 2× Me), 6.86 (1H, d, H_4', $J = 3.3$ Hz), 7.42 (1H, d, H_α, $J = 15.6$ Hz), 7.43 (1H, dd, H_5, $J = 8.2$ Hz, 1.2 Hz), 7.71 (1H, d, H_3', $J = 3.7$ Hz), 7.75 (1H, d, H_6, $J = 8.3$ Hz), 7.78 (1H, s, H_8), 8.18 (1H, d, H_β, $J = 15.6$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 327 (M^+, 3.61%), 125 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.89; H, 4.26; N, 4.25.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(2,5-dimethylthien-3-yl)prop-2-en-1-one ***(1e)*** Yield, 70%; yellow solid. mp 183–185°C. IR (KBr, cm^{-1}): 1648 (C=O), 1590 (C=C), 1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.44–2.72 (s, 3× Me), 7.10 (1H, s, H_4'), 7.32 (1H, d, H_α, $J = 15.7$ Hz), 7.41 (1H, dd, H_5, $J = 8.4$ Hz, 1.2 Hz), 7.74 (1H, d, H_6, $J = 8.3$ Hz), 7.78 (1H, s, H_8), 8.08 (1H, d, H_β, $J = 15.7$ Hz), 8.37 (1H, s, H_4). MS (*m/z*): 341 (M^+, 10.31%), 306 (M^+–Cl, 100%). Anal. Calcd for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10. Found: C, 66.65; H, 4.68; N, 4.08.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(3-chlorothien-2-yl)prop-2-en-1-one ***(1f)*** Yield, 66%; yellow solid. mp 160–162°C. IR (KBr, cm^{-1}): 1650 (C=O), 1591 (C=C), 1569 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, Me), 7.07 (1H, d, H_4', $J = 5.2$ Hz), 7.28 (1H, dd, H_5, $J = 8.3$ Hz, 1.1 Hz), 7.60 (1H, d, H_5', $J = 5.2$ Hz), 7.77 (1H, d, H_6, $J = 8.6$ Hz), 7.82 (1H, d, H_α, $J = 15.5$ Hz), 7.96 (1H, s, H_8), 8.23 (1H, d, H_β, $J = 15.5$ Hz), 8.42 (1H, s, H_4). MS (*m/z*): 347 (M^+, 1.8%), 145 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd. for $C_{17}H_{11}Cl_2NOS$: C, 58.63; H, 3.18; N, 4.02. Found: C, 58.53; H, 3.16; N, 3.97.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(5-chlorothien-2-yl)prop-2-en-1-one ***(1g)*** Yield, 80%; pale yellow solid. mp 170–171°C. IR (KBr, cm^{-1}): 1656 (C=O), 1598 (C=C), 1570 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, Me), 6.92 (1H, d, H_4', $J = 4.1$ Hz), 7.35 (1H, dd, H_5, $J = 8.3$ Hz, 1.2 Hz), 7.39 (1H, d, H_α, $J = 15.6$ Hz), 7.57 (1H, d, H_3', $J = 4.1$ Hz), 7.64 (1H, d, H_6, $J = 8.3$ Hz), 7.72 (1H, s, H_8), 8.20 (1H, d, H_β,

$J = 15.6$ Hz), 8.39 (1H, s, H_4). MS (*m/z*): 347 (M^+, 2.41%), 145 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{17}H_{11}Cl_2NOS$: C, 58.63; H, 3.18; N, 4.02. Found: C, 58.57; H, 3.14; N, 3.96.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(2,5-dichlorothien-3-yl)prop-2-en-1-one ***(1h)*** Yield, 63%; off-white solid. mp 163°C. IR (KBr, cm^{-1}): 1662 (C=O), 1596 (C=C), 1572 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, Me), 7.23 (1H, s, H_4'), 7.42 (1H, dd, H_5, $J = 8.3$ Hz, 1.0 Hz), 7.45 (1H, d, H_α, $J = 15.7$ Hz), 7.76 (1H, d, H_6, $J = 8.3$ Hz), 7.79 (1H, s, H_8), 8.15 (1H, d, H_β, $J = 15.7$ Hz), 8.39 (1H, s, H_4). MS (*m/z*): 383 (M^+, 1.7%), 346 (M^+–Cl, 100%). Anal. Calcd for $C_{17}H_{10}Cl_3NOS$: C, 53.35; H, 2.63; N, 3.66. Found: C, 53.26; H, 2.58; N, 3.67.

(2E)-1-(3-Bromothien-2-yl)-3-(2-chloro-7-methylquinolin-3-yl)prop-2-en-1-one ***(1i)*** Yield, 79%; yellow solid. mp 164–165°C. IR (KBr, cm^{-1}): 1652 (C=O), 1592 (C=C), 1568 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s, Me), 7.16 (1H, d, H_4', $J = 5.16$ Hz), 7.42 (1H, dd, H_5, $J = 8.3$ Hz, 1.3 Hz), 7.58 (1H, d, H_5', $J = 5.2$ Hz), 7.78 (1H, d, H_6, $J = 8.6$ Hz), 7.82 (1H, d, H_α, $J = 15.6$ Hz), 7.79 (1H, s, H_8), 8.23 (1H, d, H_β, $J = 15.5$ Hz), 8.43 (1H, s, H_4). MS (*m/z*): 393 (M^+, 1.5%), 82 (M^+–$C_{13}H_9NOClBr$, 100%). Anal. Calcd for $C_{17}H_{11}BrClNOS$: C, 51.99; H, 2.82; N, 3.57. Found: C, 51.94; H, 2.76; N, 3.56.

(2E)-1-(5-Bromothien-2-yl)-3-(2-chloro-7-methylquinolin-3-yl)prop-2-en-1-one ***(1j)*** Yield, 75%; yellow solid. mp 162–164°C. IR (KBr, cm^{-1}): 1653 (C=O), 1588 (C=C), 1566 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, Me), 7.16 (1H, d, H_4', $J = 4.0$ Hz), 7.38 (1H, d, H_α, $J = 15.6$ Hz), 7.42 (1H, dd, H_5, $J = 8.3$ Hz, 1.0 Hz), 7.63 (1H, d, H_3', $J = 4.0$ Hz), 7.76 (1H, d, H_6, $J = 8.3$ Hz),7.79 (1H, s, H_8), 8.21 (1H, d, H_β, $J = 15.6$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 393 (M^+, 1.5%), 82 (M^+–$C_{13}H_9NOClBr$, 100%). Anal. Calcd for $C_{17}H_{11}BrClNOS$: C, 51.99; H, 2.82; N, 3.57. Found: C, 51.95; H, 2.79; N, 3.56.

(2E)-3-(2-Chloro-7-methylquinolin-3-yl)-1-(5-iodothien-2-yl)prop-2-en-1-one ***(1k)*** Yield, 90%; deep yellow solid. mp 164–165°C. IR (KBr, cm^{-1}): 1650 (C=O), 1596 (C=C), 1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, Me), 7.36 (1H, d, H_4', $J = 4.0$ Hz), 7.37 (1H, d, H_α, $J = 15.5$ Hz), 7.42 (1H, dd, H_5, $J = 8.4$ Hz, 1.2 Hz), 7.50 (1H, d, H_3', $J = 4.0$ Hz), 7.76 (1H, d, H_6, $J = 8.3$ Hz), 7.79 (1H, s, H_8), 8.21 (1H, d, H_β, $J = 15.6$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 439 (M^+, 1.5%), 82 (M^+–$C_{13}H_9NOICl$, 100%). Anal. Calcd for $C_{17}H_{11}ClINOS$: C, 46.44; H, 2.52; N, 3.19. Found: C, 46.44; H, 2.43; N, 3.18.

(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-thien-3-ylprop-2-en-1-one ***(2a)*** Yield, 60%; pale yellow solid. mp 128–130°C. IR (KBr, cm^{-1}): 1649 (C=O), 1591 (C=C), 1561 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.39 (1H, dd, H_4', $J = 5.1$ Hz, 2.9 Hz), 7.46 (1H, d, H_α, $J = 15.6$ Hz), 7.47 (1H, t, H_6, $J = 7.6$ Hz), 7.60 (1H, d, H_7, $J = 7.0$ Hz), 7.69 (1H, d, H_5', $J = 4.7$ Hz, 1.1 Hz), 7.70 (1H, d, H_5, $J = 6.7$ Hz), 8.20 (1H, d, H_β, $J = 15.7$ Hz), 8.20 (1H, dd, H_2', $J = 2.8$ Hz, 1.1 Hz), 8.42 (1H, s, H_4). MS (*m/z*): 313 (M^+, 1.9%), 111 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{17}H_{12}ClNOS$: C, 65.07; H, 3.85; N, 4.46. Found: C, 65.04; H, 3.78; N, 4.44.

(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(3-methylthien-2-yl)prop-2-en-1-one ***(2b)*** Yield, 56%; yellow solid. mp 174–175°C. IR (KBr, cm^{-1}): 1654 (C=O), 1594 (C=C), 1563 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.66–2.76 (s, 2× Me), 7.02 (1H, d, H_4', $J = 4.9$ Hz), 7.41 (1H, d, H_α, $J = 15.4$ Hz), 7.47 (1H, t, H_6, $J = 7.6$ Hz), 7.49 (1H, d, H_5', $J = 5.3$ Hz), 7.59 (1H, d, H_7, $J = 7.0$ Hz), 7.71 (1H, d, H_5, $J = 8.0$ Hz), 8.20 (1H, d, H_β, $J = 15.4$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 327 (M^+, 6.74%), 125 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.90; H, 4.27; N, 4.27.

(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(4-methylthien-2-yl)prop-2-en-1-one ***(2c)*** Yield, 49%; yellow solid. mp 146–147°C. IR (KBr, cm^{-1}): 1655 (C=O), 1593 (C=C), 1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.33–2.76 (s, 2× Me), 7.31 (1H, s, H_5'), 7.46 (1H, d, H_α, $J = 15.5$ Hz), 7.47 (1H, t, H_6, $J = 7.6$ Hz), 7.60 (1H, d, H_7, $J = 7.0$ Hz), 7.70 (1H, d, H_5, $J = 7.0$ Hz), 7.71 (1H, s, H_3'), 8.23 (1H, d, H_β, $J = 15.6$ Hz), 8.42 (1H, s, H_4). MS (*m/z*): 327 (M^+, 5.02%), 292 (M^+–Cl, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.85; H, 4.23; N, 4.22.

(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(5-methylthien-2-yl)prop-2-en-1-one ***(2d)*** Yield, 55%; yellow solid. mp 180–181°C. IR (KBr, cm^{-1}): 1652 (C=O), 1596 (C=C), 1563 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.57–2.75 (s, 2× Me), 6.86 (1H, d, H_4', $J = 3.1$ Hz), 7.43 (1H, d, H_α, $J = 15.6$ Hz), 7.46 (1H, t, H_6, $J = 7.7$ Hz), 7.59 (1H, d, H_7, $J = 7.0$ Hz), 7.69 (1H, d, H_5, $J = 8.2$ Hz), 7.72 (1H, d, H_3', $J = 3.8$ Hz), 8.19 (1H, d, H_β, $J = 15.6$ Hz), 8.40 (1H, s, H_4). MS (*m/z*): 327 (M^+, 5.56%), 125 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.30; N, 4.27. Found: C, 65.86; H, 4.25; N, 4.25.

(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(2,5-dimethylthien-3-yl)prop-2-en-1-one ***(2e)*** Yield, 67%; yellow solid. mp 138–140°C. IR (KBr, cm^{-1}): 1648 (C=O), 1585 (C=C),

1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.44–2.75 (s, 3× Me), 7.10 (1H, s, H_4'), 7.33 (1H, d, H_α, $J = 15.7$ Hz), 7.46 (1H, t, H_6, $J = 7.7$ Hz), 7.59 (1H, d, H_7, $J = 7.0$ Hz), 7.68 (1H, d, H_5, $J = 8.1$ Hz), 8.10 (1H, d, H_β, $J = 15.7$ Hz), 8.37 (1H, s, H_4). MS (*m/z*): 341 (M^+, 7.71%), 139 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10. Found: C, 66.66; H, 4.62; N, 4.02.

*(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(3-chlorothien-2-yl)prop-2-en-1-one (**2f**)* Yield, 73%; yellow solid. mp 162–163°C. IR (KBr, cm^{-1}): 1650 (C=O), 1592 (C=C), 1570 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.07 (1H, d, H_4', $J = 5.3$ Hz), 7.47 (1H, t, H_6, $J = 7.7$ Hz), 7.59 (1H, d, H_7, $J = 7.0$ Hz), 7.60 (1H, d, H_5', $J = 5.3$ Hz), 7.71 (1H, d, H_5, $J = 8.1$ Hz), 7.82 (1H, d, H_α, $J = 15.5$ Hz), 8.24 (1H, d, H_β, $J = 15.6$ Hz), 8.42 (1H, s, H_4). MS (*m/z*): 347 (M^+, 1.18%), 145 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd. for $C_{17}H_{11}Cl_2NOS$: C, 58.63; H, 3.18; N, 4.02. Found: C, 58.59; H, 3.12; N, 3.98.

*(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(5-chlorothien-2-yl) prop-2-en-1-one (**2g**)* Yield, 85%; pale yellow solid. mp 166–168°C. IR (KBr, cm^{-1}): 1656 (C=O), 1598 (C=C), 1572 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.02 (1H, d, H_4', $J = 4.0$ Hz), 7.39 (1H, d, H_α, $J = 15.5$ Hz), 7.48 (1H, t, H_6, $J = 7.6$ Hz), 7.61 (1H, d, H_7, $J = 7.0$ Hz), 7.68 (1H, d, H_3', $J = 4.2$ Hz), 7.70 (1H, d, H_5, $J = 8.1$ Hz), 8.23 (1H, d, H_β, $J = 15.6$ Hz), 8.41 (1H, s, H_4). MS (*m/z*): 347 (M^+–Cl, 1.24%), 145 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{17}H_{11}Cl_2NOS$: C, 58.63; H, 3.18; N, 4.02. Found: C, 58.55; H, 3.13; N, 3.97.

*(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(2,5-dichlorothien-3-yl)prop-2-en-1-one (**2h**)* Yield, 69%; colourless solid. mp 120–121°C. IR (KBr, cm^{-1}): 1664 (C=O), 1596 (C=C), 1570 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.15 (1H, s, H_4'), 7.45 (1H, d, H_α, $J = 15.7$ Hz), 7.47 (1H, t, H_6, $J = 7.7$ Hz), 7.61 (1H, d, H_7, $J = 6.8$ Hz), 7.70 (1H, d, H_5, $J = 8.1$ Hz), 8.17 (1H, d, H_β, $J = 15.7$ Hz), 8.39 (1H, s, H_4). MS (*m/z*): 383 (M^+, 1.8%), 179 (M^+–$C_{12}H_9NCl$, 100%). Anal. Calcd for $C_{17}H_{10}Cl_3NOS$: C, 53.35; H, 2.63; N, 3.66. Found: C, 53.24; H, 2.55; N, 3.60.

*(2E)-1-(3-Bromothien-2-yl)-3-(2-chloro-8-methylquinolin-3-yl) prop-2-en-1-one (**2i**)* Yield, 86%; yellow solid. mp 210–212°C. IR (KBr, cm^{-1}): 1652 (C=O), 1592 (C=C), 1568 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.16 (1H, d, H_4', $J = 5.2$ Hz), 7.47 (1H, t, H_6, $J = 7.6$ Hz), 7.58 (1H, d, H_5', $J = 5.2$ Hz), 7.60 (1H, d, H_7, $J = 7.1$ Hz), 7.71 (1H, d, H_5, $J = 8.0$ Hz), 7.81 (1H, d, H_α, $J = 15.6$ Hz), 8.25 (1H, d, H_β, $J = 15.5$ Hz), 8.44 (1H, s, H_4). MS (*m/z*): 393 (M^+, 1.0%), 82 (M^+–$C_{13}H_9NOClBr$, 100%). Anal. Calcd. for $C_{17}H_{11}BrClNOS$: C, 51.99; H, 2.82; N, 3.57. Found: C, 51.98; H, 2.77; N, 3.59.

*(2E)-1-(5-Bromothien-2-yl)-3-(2-chloro-8-methylquinolin-3-yl) prop-2-en-1-one (**2j**)* Yield, 71%; off-white solid. mp 204–206°C. IR (KBr, cm^{-1}): 1653 (C=O), 1588 (C=C), 1566 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.17 (1H, d, H_4', $J = 4.0$ Hz), 7.39 (1H, d, H_α, $J = 15.6$ Hz), 7.48 (1H, t, H_6, $J = 7.6$ Hz), 7.61 (1H, d, H_7, $J = 7.1$ Hz), 7.63 (1H, d, H_3', $J = 4.0$ Hz), 7.70 (1H, d, H_5, $J = 8.0$ Hz), 8.23 (1H, d, H_β, $J = 15.6$ Hz), 8.41 (1H, s, H_4). MS (*m/z*): 393 (M^+, 2%), 82 (M^+–$C_{13}H_9NOClBr$, 100%). Anal. Calcd for $C_{17}H_{11}BrClNOS$: C, 51.99; H, 2.82; N, 3.57. Found: C, 51.93; H, 2.75; N, 3.55.

*(2E)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(5-iodothien-2-yl)prop-2-en-1-one (**2k**)* Yield, 86%; yellow solid. mp 196–198°C. IR (KBr, cm^{-1}): 1649 (C=O), 1596 (C=C), 1565 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, Me), 7.36 (1H, d, H_4', $J = 3.8$ Hz), 7.38 (1H, d, H_α, $J = 15.6$ Hz), 7.47 (1H, t, H_6, $J = 7.6$ Hz), 7.51 (1H, d, H_3', $J = 3.9$ Hz), 7.61 (1H, d, H_7, $J = 7.0$ Hz), 7.70 (1H, d, H_5, $J = 8.1$ Hz), 8.23 (1H, d, H_β, $J = 15.6$ Hz), 8.41 (1H, s, H_4). MS (*m/z*): 439 (M^+, 1%), 82 (M^+–$C_{13}H_9NOICl$, 100%). Anal. Calcd for $C_{17}H_{11}ClINOS$: C, 46.44; H, 2.52; N, 3.19. Found: C, 46.39; H, 2.42; N, 3.13.

*General procedure for the preparation of 2-chloro-3-[3-(aryl)-4,5-dihydro-1H-pyrazol-5-yl]-7/8-methylquinoline (**3a–k**) and (**4a–k**)*

A mixture of chalcone (**1a–k** or **2a–k,** 1.0 mmol) and hydrazine hydrate (3.0 mmol) in ethanol (10 ml) was refluxed. The crude product got precipitated within 8–15 min which was poured onto ice-cold water (50 ml). The precipitates were collected by filtration, washed with cold water followed by cold EtOH to obtain 2-pyrazolines which were recrystallised from EtOH (95%) to obtain pure compounds (**3a–k** and **4a–k**).

*2-Chloro-7-methyl-3-(3-thiophen-3-yl-4,5-dihydro-1H-pyrazol-5-yl)quinoline (**3a**)* Yield, 80%; colourless solid. mp 180–181°C. IR (KBr, cm^{-1}): 3275 (NH), 1596 (C=N of pyrazoline ring), 1555 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s, CH_3), 2.95 (1H, dd, $J = 16.3$, 9.4 Hz, 4-H_a), 3.74 (1H, dd, $J = 16.4$, 10.6 Hz, 4-H_b), 5.38 (1H, t, $J = 9.9$ Hz, 5-H), 7.31 (1H, dd, H_4', $J = 5.0$ Hz, 2.8 Hz), 7.40 (1H, d, H_5, $J = 8.1$ Hz), 7.62 (1H, dd, H_5', $J = 4.9$ Hz, 0.9 Hz), 7.73 (1H, d, H_6, $J = 8.3$ Hz), 7.75

(1H, s, H_8), 8.08 (1H, dd, H_2', $J = 2.8$ Hz, 1.0 Hz), 8.40 (1H, s, H_4). MS (*m/z*): 327 (M^+, 78.53%). Anal. Calcd for $C_{17}H_{14}ClN_3S$: C, 62.28; H, 4.30; N, 12.82. Found: C, 62.24; H, 4.25; N, 12.80.

*2-Chloro-7-methyl-3-[3-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**3b**)* Yield, 78%; yellow solid. mp 160–161°C. IR (KBr, cm^{-1}): 3285 (NH), 1602 (C=N of pyrazoline ring), 1559 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.53–2.62 (s, 2× CH_3), 2.84 (1H, dd, $J = 16.3$, 9.4 Hz, 4-H_a), 3.64 (1H, dd, $J = 16.3$, 10.4 Hz, 4-H_b), 5.29 (1H, t, $J = 9.9$ Hz, 5-H), 6.82 (1H, d, H_4', $J = 5.0$ Hz), 7.35 (1H, d, H_5, $J = 8.1$ Hz), 7.35 (1H, d, H_5', $J = 4.9$ Hz), 7.74 (1H, d, H_6, $J = 8.5$ Hz), 7.76 (1H, s, H_8), 8.39 (1H, s, H_4). MS (*m/z*): 341 (M^+, 84.01%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.14; H, 4.65; N, 12.29.

*2-Chloro-7-methyl-3-[3-(4-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**3c**)* Yield, 83%; colourless solid. mp 200°C. IR (KBr, cm^{-1}): 3280 (NH), 1599 (C=N of pyrazoline ring), 1555 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.30–2.50 (s, 2× CH_3), 2.85 (1H, dd, $J = 16.3$, 9.3 Hz, 4-H_a), 3.66 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.30 (1H, t, $J = 9.9$ Hz, 5-H), 7.11 (1H, s, H_5'), 7.37 (1H, d, H_5, $J = 8.1$ Hz), 7.51 (1H, s, H_3'), 7.74 (1H, d, H_6, $J = 8.3$ Hz), 7.76 (1H, s, H_8), 8.41 (1H, s, H_4). MS (*m/z*): 341 (M^+, 84.02%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.21; H, 4.69; N, 12.25.

*2-Chloro-7-methyl-3-[3-(5-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**3d**)* Yield, 87%; pale yellow solid. mp 198°C. IR (KBr, cm^{-1}): 3275 (NH), 1595 (C=N of pyrazoline ring), 1558 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52–2.54 (s, 2× CH_3), 2.85 (1H, dd, $J = 16.3$, 9.3 Hz, 4-H_a), 3.66 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.31 (1H, t, $J = 9.9$ Hz, 5-H), 6.66 (1H, d, H_4', $J = 3.2$ Hz), 6.85 (1H, d, H_3', $J = 3.5$ Hz), 7.37 (1H, d, H_5, $J = 8.1$ Hz), 7.74 (1H, d, H_6, $J = 8.3$ Hz), 7.76 (1H, s, H_8), 8.40 (1H, s, H_4). MS (*m/z*): 341 (M^+, 84.04%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.23; H, 4.69; N, 12.31.

*2-Chloro-3-[3-(2,5-dimethylthiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl]-7-methylquinoline (**3e**)* Yield, 86%; off-white solid. mp 116–117°C. IR (KBr, cm^{-1}): 3279 (NH), 1610 (C=N of pyrazoline ring), 1556 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.36–2.65 (s, 3× CH_3), 2.82 (1H, dd, $J = 16.2$, 9.7 Hz, 4-H_a), 3.65 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.28 (1H, t, $J = 10.0$ Hz, 5-H), 6.86 (1H, s, H_4'), 7.41 (1H, d, H_5, $J = 8.3$ Hz), 7.72 (1H, d, H_6, $J = 8.3$ Hz), 7.76 (1H, s, H_8), 8.34 (1H, s, H_4). MS (*m/z*): 355 (M^+, 100%). Anal. Calcd. for $C_{19}H_{18}ClN_3S$: C, 64.12; H, 5.10; N, 11.81. Found: C, 64.08; H, 5.05; N, 11.76.

*2-Chloro-3-[3-(3-chlorothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-7-methylquinoline (**3f**)* Yield, 79%; colourless solid. mp 166167°C. IR (KBr, cm^{-1}): 3288 (NH), 1608 (C=N of pyrazoline ring), 1560 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.15 (1H, dd, $J = 16.9$, 10.1 Hz, 4-H_a), 4.00 (1H, dd, $J = 16.9$, 10.8 Hz, 4-H_b), 5.39 (1H, t, $J = 10.4$ Hz, 5-H), 6.86 (1H, d, H_4', $J = 5.2$ Hz), 7.21 (1H, d, H_5, $J = 8.3$ Hz), 7.32 (1H, d, H_5', $J = 5.2$ Hz), 7.76 (1H, d, H_6, $J = 8.6$ Hz), 7.89 (1H, s, H_8), 8.37 (1H, s, H_4). MS (*m/z*): 361 (M^+, 96.20%) 185 (M^+–$C_{10}H_7NCl$, 100%). Anal. Calcd. for $C_{17}H_{13}Cl_2N_3S$: C, 56.36; H, 3.62; N, 11.60. Found: C, 56.32; H, 3.61; N, 11.58.

*2-Chloro-3-[3-(5-chlorothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-7-methylquinoline (**3g**)* Yield, 83%; off-white solid. mp 205–207°C. IR (KBr, cm^{-1}): 3284 (NH), 1605 (C=N of pyrazoline ring), 1560 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s, CH_3), 2.87 (1H, dd, $J = 16.2$, 10.0 Hz, 4-H_a), 3.71 (1H, dd, $J = 16.2$, 10.7 Hz, 4-H_b), 5.36 (1H, t, $J = 10.3$ Hz, 5-H), 6.82 (1H, d, H_4', $J = 4.3$ Hz), 7.28 (1H, d, H_5, $J = 8.3$ Hz), 7.47 (1H, d, H_3', $J = 4.3$ Hz), 7.65 (1H, d, H_6, $J = 8.3$ Hz), 7.69 (1H, s, H_8), 8.34 (1H, s, H_4). MS (*m/z*): 361 (M^+, 100%). Anal. Calcd for $C_{17}H_{13}Cl_2N_3S$: C, 56.36; H, 3.62; N, 11.60. Found: C, 56.34 H, 3.59; N, 11.52.

*2-Chloro-3-[3-(2,5-dichlorothiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl]-7-methylquinoline (**3h**)* Yield, 75%; off-white solid. mp 178–179°C. IR (KBr, cm^{-1}): 3282 (NH), 1612 (C=N of pyrazoline ring), 1561 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.11 (1H, dd, $J = 16.7$, 9.9 Hz, 4-H_a), 3.98 (1H, dd, $J = 16.7$, 10.5 Hz, 4-H_b), 5.39 (1H, t, $J = 10.2$ Hz, 5-H), 6.97 (1H, s, H_4'), 7.35 (1H, d, H_5, $J = 8.3$ Hz), 7.72 (1H, d, H_6, $J = 8.2$ Hz), 7.75 (1H, s, H_8), 8.33 (1H, s, H_4). MS (*m/z*): 397 (M^+, 100%). Anal. Calcd. for $C_{17}H_{12}Cl_3N_3S$: C, 51.47; H, 3.05; N, 10.59. Found: C, 51.45; H, 3.02; N, 10.54.

*3-[3-(3-Bromothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-2-chloro-7-methylquinoline (**3i**)* Yield, 92%; colourless solid. mp 170–171°C; IR (KBr, cm^{-1}): 3279 (NH), 1608 (C=N of pyrazoline ring), 1556 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.19 (1H, dd, $J = 16.8$, 10.1 Hz, 4-H_a), 4.06 (1H, dd, $J = 16.8$, 10.8 Hz, 4-H_b), 5.39 (1H, t, $J = 10.4$ Hz, 5-H), 6.95 (1H, d, H_4', $J = 5.5$ Hz), 7.35 (1H, d, H_5, $J = 8.2$ Hz), 7.21 (1H, d, H_5', $J = 5.5$ Hz), 7.72 (1H, d, H_6, $J = 8.6$ Hz), 7.74 (1H,

s, H_8), 8.38 (1H, s, H_4). MS (*m/z*): 407 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}BrClN_3S$: C, 50.20; H, 3.22; N, 10.33. Found: C, 50.12; H, 3.14; N, 10.30.

*3-[3-(5-Bromothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-2-chloro-7-methylquinoline (**3j**)* Yield, 76%; colourless solid. mp 195°C. IR (KBr, cm^{-1}): 3282 (NH), 1600 (C=N of pyrazoline ring), 1552 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3), 2.88 (1H, dd, $J = 16.2$, 9.9 Hz, 4-H_a), 3.71 (1H, dd, $J = 16.2$, 10.7 Hz, 4-H_b), 5.36 (1H, t, $J = 10.3$ Hz, 5-H), 6.86 (1H, d, H_4', $J = 4.2$ Hz), 7.36 (1H, d, H_5, $J = 8.3$ Hz), 7.43 (1H, d, H_3', $J = 4.2$ Hz), 7.74 (1H, d, H_6, $J = 8.3$ Hz), 7.75 (1H, s, H_8), 8.35 (1H, s, H_4). MS (*m/z*): 407 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}BrClN_3S$: C, 50.20; H, 3.22; N, 10.33. Found: C, 50.15; H, 3.19; N, 10.25.

*2-Chloro-3-[3-(5-iodothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-7-methylquinoline (**3k**)* Yield, 85%; colourless solid. mp 212°C. IR (KBr, cm^{-1}): 3281 (NH), 1610 (C=N of pyrazoline ring), 1550 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3), 2.87 (1H, dd, $J = 16.2$, 9.9 Hz, 4-H_a), 3.71 (1H, dd, $J = 16.2$, 10.7 Hz, 4-H_b), 5.36 (1H, t, $J = 10.3$ Hz, 5-H), 6.71 (1H, d, H_4', $J = 4.2$ Hz), 7.15 (1H, d, H_3', $J = 4.2$ Hz), 7.34 (1H, d, H_5, $J = 8.4$ Hz), 7.74 (1H, d, H_6, $J = 8.3$ Hz), 7.75 (1H, s, H_8), 8.35 (1H, s, H_4). MS (*m/z*): 453 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}ClIN_3S$: C, 45.00; H, 2.89; N, 9.26. Found: C, 44.95; H, 2.85; N, 9.23.

*2-Chloro-8-methyl-3-(3-thiophen-3-yl-4,5-dihydro-1H-pyrazol-5-yl)quinoline (**4a**)* Yield, 72%; colourless solid. mp 195–196°C. IR (KBr, cm^{-1}): 3274 (NH), 1595 (C=N of pyrazoline ring), 1550 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, CH_3), 2.97 (1H, dd, $J = 16.4$, 9.4 Hz, 4-H_a), 3.75 (1H, dd, $J = 16.4$, 10.7 Hz, 4-H_b), 5.39 (1H, t, $J = 9.9$ Hz, 5-H), 7.32 (1H, dd, H_4', $J = 5.0$ Hz, 2.8 Hz), 7.45 (1H, t, H_6, $J = 7.6$ Hz), 7.55 (1H, d, H_7, $J = 7.0$ Hz), 7.60 (1H, d, H_5', $J = 4.6$ Hz, 1.0 Hz), 7.67 (1H, d, H_5, $J = 6.6$ Hz), 8.08 (1H, dd, H_2', $J = 2.7$ Hz, 1.0 Hz), 8.39 (1H, s, H_4). MS (*m/z*): 327 (M^+, 70.30%). Anal. Calcd. for $C_{17}H_{14}ClN_3S$: C, 62.28; H, 4.30; N, 12.82. Found: C, 62.22; H, 4.22; N, 12.78.

*2-Chloro-8-methyl-3-[3-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**4b**)* Yield, 67%; colourless solid. mp 130–131°C. IR (KBr, cm^{-1}): 3277 (NH), 1605 (C=N of pyrazoline ring), 1552 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.63–2.73 (s, 2× CH_3), 2.85 (1H, dd, $J = 16.3$, 9.4 Hz, 4-H_a), 3.66 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.31 (1H, t, $J = 9.9$ Hz, 5-H),6.82 (1H, d, H_4', $J = 5.1$ Hz), 7.45 (1H, t, H_6, $J = 7.6$ Hz), 7.33 (1H, d, H_5', $J = 5.1$ Hz), 7.54 (1H, d, H_7, $J = 7.0$ Hz), 7.69 (1H, d, H_5, $J = 7.9$ Hz), 8.38 (1H, s, H_4). MS (*m/z*): 341 (M^+, 59.47%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.22; H, 4.75; N, 12.23.

*2-Chloro-8-methyl-3-[3-(4-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**4c**)* Yield, 71%; colourless solid. mp 182°C. IR (KBr, cm^{-1}): 3281 (NH), 1595 (C=N of pyrazoline ring), 1555 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.30–2.72 (s, 2× CH_3), 2.87 (1H, dd, $J = 16.3$, 9.3 Hz, 4-H_a), 3.69 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.31 (1H, t, $J = 9.9$ Hz, 5-H) 7.11 (1H, s, H_5'), 7.44 (1H, t, H_6, $J = 7.5$ Hz), 7.55 (1H, d, H_7, $J = 7.0$ Hz), 7.69 (1H, d, H_5, $J = 7.0$ Hz), 7.52 (1H, s, H_3'), 8.37 (1H, s, H_4). MS (*m/z*): 341 (M^+, 60.02%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.20; H, 4.69; N, 12.25.

*2-Chloro-8-methyl-3-[3-(5-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (**4d**)* Yield, 80%; pale yellow solid. mp 209–210°C. IR (KBr, cm^{-1}): 3278 (NH), 1592 (C=N of pyrazoline ring), 1550 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.53–2.72 (s, 2× CH_3), 2.86 (1H, dd, $J = 16.3$, 9.3 Hz, 4-H_a), 3.67 (1H, dd, $J = 16.3$, 10.5 Hz, 4-H_b), 5.31 (1H, t, $J = 9.9$ Hz, 5-H), 6.66 (1H, d, H_4', $J = 3.0$ Hz), 6.86 (1H, d, H_3' $J = 3.4$ Hz), 7.44 (1H, t, H_6, $J = 7.6$ Hz), 7.54 (1H, d, H_7, $J = 7.0$ Hz), 7.62 (1H, d, H_5, $J = 8.1$ Hz), 8.33 (1H, s, H_4). MS (*m/z*): 341 (M^+, 59.81%). Anal. Calcd. for $C_{18}H_{16}ClN_3S$: C, 63.24; H, 4.72; N, 12.29. Found: C, 63.23; H, 4.70; N, 12.27.

*2-Chloro-3-[3-(2,5-dimethylthiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl]-8-methylquinoline (**4e**)* Yield, 88%; brown solid. mp 126–127°C. IR (KBr, cm^{-1}): 3282 (NH), 1609 (C=N of pyrazoline ring), 1553 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.42–2.73 (s, 3× Me), 2.84 (1H, dd, $J = 16.3$, 9.7 Hz, 4-H_a), 3.68 (1H, dd, $J = 16.3$, 10.6 Hz, 4-H_b), 5.30 (1H, t, $J = 10.0$ Hz, 5-H), 6.86 (1H, s, H_4'), 7.42 (1H, t, H_6, $J = 7.7$ Hz), 7.54 (1H, d, H_7, $J = 7.0$ Hz), 7.68 (1H, d, H_5, $J = 8.1$ Hz), 8.34 (1H, s, H_4). MS (*m/z*): 355 (M^+, 100%). Anal. Calcd. for $C_{19}H_{18}ClN_3S$: C, 64.12; H, 5.10; N, 11.81. Found: C, 64.10; H, 5.08; N, 11.79.

*2-Chloro-3-[3-(3-chlorothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-8-methylquinoline (**4f**)* Yield, 81%; yellowish brown solid. mp 152°C. IR (KBr, cm^{-1}): 3277 (NH), 1610 (C=N of pyrazoline ring), 1559 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 3.16 (1H, dd, $J = 16.9$, 10.2 Hz, 4-H_a), 4.01 (1H, dd, $J = 16.9$, 10.8 Hz, 4-H_b), 5.39 (1H, t, $J = 10.4$ Hz, 5-H), 6.87 (1H, d, H_4', $J = 5.4$ Hz), 7.41 (1H, t, H_6, $J = 7.6$ Hz), 7.54 (1H, d, H_7, $J = 7.0$ Hz), 7.32 (1H, d, H_5', $J = 5.4$ Hz), 7.65 (1H, d,

H_5, $J = 8.1$ Hz), 8.37 (1H, s, H_4). MS (*m/z*): 361 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}Cl_2N_3S$: C, 56.36; H, 3.62; N, 11.60. Found: C, 56.34; H, 3.58; N, 11.54.

2-Chloro-3-[3-(5-chlorothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-8-methylquinoline ***(4g)*** Yield, 80%; pale yellow solid. mp 230–232°C. IR (KBr, cm^{-1}): 3285 (NH), 1603 (C=N of pyrazoline ring), 1560 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 2.89 (1H, dd, $J = 16.3$, 10.1 Hz, 4-H_a), 3.71 (1H, dd, $J = 16.3$, 10.7 Hz, 4-H_b), 5.39 (1H, t, $J = 10.3$ Hz, 5-H), 6.85 (1H, d, H_4', $J = 4.2$ Hz), 7.42 (1H, t, H_6, $J = 7.6$ Hz), 7.56 (1H, d, H_7, $J = 7.0$ Hz), 7.48 (1H, d, H_3', $J = 4.4$ Hz), 7.63 (1H, d, H_5, $J = 8.0$ Hz), 8.35 (1H, s, H_4). MS (*m/z*): 361 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}Cl_2N_3S$: C, 56.36; H, 3.62; N, 11.60. Found: C, 56.31; H, 3.56; N, 11.55.

2-Chloro-3-[3-(2,5-dichlorothiophen-3-yl)-4,5-dihydro-1H-pyrazol-5-yl]-8-methylquinoline ***(4h)*** Yield, 75%; yellowish brown solid. mp 153°C. IR (KBr, cm^{-1}): 3280 (NH), 1615 (C=N of pyrazoline ring), 1560 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 3.15 (1H, dd, $J = 16.8$, 10.0 Hz, 4-H_a), 4.00 (1H, dd, $J = 16.8$, 10.5 Hz, 4-H_b), 5.40 (1H, t, $J = 10.3$ Hz, 5-H), 6.96 (1H, s, H_4'), 7.41 (1H, t, H_6, $J = 7.6$ Hz), 7.56 (1H, d, H_7, $J = 6.8$ Hz), 7.62 (1H, d, H_5, $J = 8.1$ Hz), 8.35 (1H, s, H_4). MS (*m/z*): 397 (M^+, 100%). Anal. Calcd. for $C_{17}H_{12}Cl_3N_3S$: C, 51.47; H, 3.05; N, 10.59. Found: C, 51.41; H, 3.00; N, 10.56.

3-[3-(3-Bromothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-2-chloro-8-methylquinoline ***(4i)*** Yield, 77%; pale yellow solid. mp 166–168°C. IR (KBr, cm^{-1}): 3279 (NH), 1607 (C=N of pyrazoline ring), 1555 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 3.21 (1H, dd, $J = 16.9$, 10.2 Hz, 4-H_a), 4.10 (1H, dd, $J = 16.8$, 10.8 Hz, 4-H_b), 5.40 (1H, t, $J = 10.4$ Hz, 5-H), 6.86 (1H, d, H_4', $J = 5.5$ Hz), 7.43 (1H, t, H_6, $J = 7.6$ Hz), 7.21 (1H, d, H_5', $J = 5.5$ Hz), 7.54 (1H, d, H_7, $J = 7.1$ Hz), 7.65 (1H, d, H_5, $J = 8.0$ Hz), 8.39 (1H, s, H_4). MS (*m/z*): 407 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}BrClN_3S$: C, 50.20; H, 3.22; N, 10.33. Found: C, 50.14; H, 3.18; N, 10.29.

3-[3-(5-Bromothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-2-chloro-8-methylquinoline ***(4j)*** Yield, 80%; pale yellow solid. mp 215–216°C. IR (KBr, cm^{-1}): 3282 (NH), 1597 (C=N of pyrazoline ring), 1552 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 2.89 (1H, dd, $J = 16.2$, 9.9 Hz, 4-H_a), 3.71 (1H, dd, $J = 16.2$, 10.6 Hz, 4-H_b), 5.36 (1H, t, $J = 10.3$ Hz, 5-H), 6.87 (1H, d, H_4', $J = 4.2$ Hz), 7.42 (1H, t, H_6, $J = 7.6$ Hz), 7.55 (1H, d, H_7, $J = 7.1$ Hz), 7.43 (1H, d, H_3', $J = 4.2$ Hz), 7.63 (1H, d, H_5, $J = 8.0$ Hz), 8.36 (1H, s, H_4). MS (*m/z*): 407 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}BrClN_3S$: C, 50.20; H, 3.22; N, 10.33. Found: C, 50.19 H, 3.17; N, 10.28.

2-Chloro-3-[3-(5-iodothiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]-8-methylquinoline ***(4k)*** Yield, 82%; pale yellow solid. mp 178°C. IR (KBr, cm^{-1}): 3280 (NH), 1605 (C=N of pyrazoline ring), 1550 (C=N of quinoline ring). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, CH_3), 2.90 (1H, dd, $J = 16.3$, 9.9 Hz, 4-H_a), 3.73 (1H, dd, $J = 16.3$, 10.6 Hz, 4-H_b), 5.37 (1H, t, $J = 10.2$ Hz, 5-H), 6.71 (1H, d, H_4', $J = 4.0$ Hz), 7.42 (1H, t, H_6, $J = 7.6$ Hz), 7.16 (1H, d, H_3', $J = 4.1$ Hz), 7.56 (1H, d, H_7, $J = 7.0$ Hz), 7.63 (1H, d, H_5, $J = 8.1$ Hz), 8.36 (1H, s, H_4). MS (*m/z*): 453 (M^+, 100%). Anal. Calcd. for $C_{17}H_{13}ClIN_3S$: C, 45.00; H, 2.89; N, 9.26. Found: C, 44.98; H, 2.81; N, 9.25.

In vitro antileishmanial assay

The title compounds (**1a–k** and **2a–k**) and (**3a–k** and **4a–k**) were tested for the antileishmanial activity using *L. major* promastigotes as parasites for in vitro screening. Parasites were cultured at 24°C in shaking incubator on M 199 medium containing foetal bovine serum (10%); HEPES (25 mM), and penicillin and streptomycin (0.22 µg each) (Ali *et al*., 1997).

Each compound (1 mg) was dissolved in DMSO (1 ml) and Amphotericin B (1 mg) taken in DMSO (1 ml) was used as a positive control. Parasites were taken from lag phase of their growth and were centrifuged at 3000 rpm for 3 min. The parasite density was maintained at 2×10^6 cells/ml by diluting with fresh culture medium. In 96-well plates, 180 µl of medium was added in different wells. The experimental compound (20 µl) was added in medium and serially diluted. Parasite culture (100 µl) was added in all wells. In negative controls, DMSO was serially diluted in medium; while the positive control, contained varying concentrations of standard antileishmanial compound, i.e. Amphotercin B. The plates were incubated for 72 h at 24°C. The culture was examined microscopically on an improved neubaur counting chamber and IC_{50} values of compounds possessing antileishmanial activity were calculated. All assays were run in duplicate. The results are summarized in Table 2. IC_{50} values of compounds were determined using prism windows-based software.

After running the samples, % of inhibition is calculated in serial dilution methods. It depends on the activity of the compounds; some of them show in 4-6-7 or 10 dilution the inhibitory concentration. Subsequently, we count the number of parasite in neubauer chamber (0.0025 mm^2) and implement the result manually in the prism windows-based software.

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